Remarks

Claims 41-60 are pending in the present application and remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Salhoff *et al.*, in view of Bundgaard (WO88/01615) (Bundgaard I) and Wang *et al.*, *Curr. Med. Chem.*,4, 437-453(2000) (Wang). The stated objective of the present invention is to provide monoesters of (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid which provide improved bioavailability of the parent monoacid in a patient. (U.S. Patent Application 10/511,452, page 1, line 17-19) Further, the present invention is specifically drawn to simple monoester prodrugs bearing a C_1-C_{10} alkyl group (or C_2-C_{10} alkyl) on the carboxyl residue at the 3-position of the decahydroisoquinoline core. Applicant respectfully submits that rejection of the pending claims is inappropriate on the ground that the cited art, when taken as a whole, fails to establish that the subject matter of the present invention is *prima facie* obvious.

As noted by the Examiner, the *Graham* factual inquiries, including (1) determining the scope and content of the prior art and (2) ascertaining the differences between the prior art and the claims at issue, provide the background for an obviousness analysis under 35 USC 103. Faced with this background, however, the burden remains on the Patent Office to show a *prima facia* case of obviousness, which requires: (1) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) a teaching or suggestion of all claim limitations. M.P.E.P. §2143.

Salhoff *et al.* discloses *in vitro* and *in vivo* pharmacology for (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid. However, as noted by the Examiner, Salhoff expressly does not teach the ester off the carboxyl residue at the three position of the decahydroisoquinoline core. (Official Action, date February 3, 2006). The Examiner has thus relied on Bundgaard I as allegedly teaching any and all ester prodrug formulations. (Official Action, date July 25, 2006). Bundgaard I generally discloses a wide variety of approaches that have been employed in an attempt to improve the bioavailability characteristics of carboxylic acid drugs, including aliphatic esters, aromatic esters, acyloxyalkyl double esters, and alkoxycarbonyloxyalkyl double esters. Notably, however, regarding simple alkyl esters of the type of the present invention, Bundgaard I explicitly states:

> *several aliphatic or aromatic esters of carboxylic acid drugs are not sufficiently labile in vivo to ensure a sufficiently high rate and extent of prodrug conversion. For example simple alkyl and aryl esters of penicillins are not hydrolyzed to active free penicillin acid in vivo. . . and therefore have no therapeutic potential . . . Similarly, the much reduced anti-inflammatory activity observed for the methyl or ethyl esters of naproxen . . . and fenbufen . . . relative to the free acids may be ascribed to the resistance of the esters to be hydrolyzed in vivo. . . . Pentopril is another ethyl ester prodrug of an angiotensin-converting enzyme inhibitor which also is highly stable in human plasma. In this case less than 50% of an oral dose of the prodrug appears to be deesterified to the active parent acid.*

WO 88/01615 (page 2, line 18 through page 3, line 9)(citations omitted). From Bundgaard I, one skilled in the art would conclude that it is highly unpredictable whether a simple alkyl ester prodrug will be converted to drug *in vivo*.

In view of the art recognized limitations associated with simple alkyl ester prodrug approaches, Bundgaard I teaches away from the present invention by instead expressly teaching highly functionalized esters comprising an (N,N-disubstituted-amido)alkyl moiety as a means for improving the bioavailability of carboxylic acid–derivative drugs. Combining the reference teachings of Salhoff with those of Bundgaard I would not lead to the esters of the present invention, but rather the highly functionalized esters comprising an (N,N-disubstituted-amido)alkyl moiety. Furthermore, in view of the express teachings of Bundgaard I, quoted above, that such esters are often not sufficiently labile *in vivo*, even if one skilled in the art were to proceed with the preparation of simple alkyl esters of the type of the present invention, there would be no reasonable expectation that such esters would improve the bioavailability of (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.

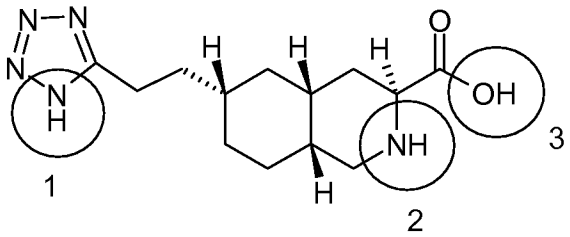
Wang has also been cited for the proposition that prodrug technology has improved to include simple alkyl esters of the type of the present invention. However, Wang discloses a variety of prodrug approaches that have been employed for the purpose of increasing the oral activity of RGD peptidomimetic analogs including: simple alkyl esters; double amidoxime ester prodrugs; double carbamoyl ethyl ester prodrugs; triple prodrugs (acetate-carbamoyl-alkyl esters, carbamoyl-dialkyl esters, and hydroxyl-dialkyl esters); and coumarin based cyclic prodrugs. Notably, Wang states that the difficulty in developing orally active RGD analogs stems in part from the intrinsic need for such molecules to have ionizable carboxyl and amino groups in order to retain bioactivity. These ionizable groups limit the membrane permeability of RGD analogs and, thus, their oral bioactivity. (see Wang at pp. 437-438). Regarding simple alkyl monoester prodrugs, Wang discloses methyl and ethyl ester prodrugs

that have been used to improve oral bioavailability of certain RGD analogs. However, Wang then expressly states

> *in many other cases, the masking of only the carboxyl group of an RGD analog was not sufficient because the ionizable amino group also contributes significantly to the charge and polarity and, therefore, low membrane permeability of an RGD analog*

Wang (p. 441, column 2, lines 23-28). Thus, from Wang, one skilled in the art would conclude that it is highly unpredictable whether a simple alkyl ester prodrug, which contains additional ionizable groups, will be sufficiently bioavailable *in vivo*.

Applicant respectfully reiterates that the objective of the present invention is to provide monoesters of (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid that increase bioavailability of the parent drug. Notably, this carboxylic acid drug contains three ionizable functional groups, namely an ionizable carboxyl group and two ionizable amino groups:



In view of the art-recognized limitations associated with masking only the carboxy-terminal functional group of molecules with additional ionizable groups, Wang teaches away from the present invention by suggesting prodrug approaches that mask both the amino and carboxy groups. As an example of this approach, Wang first teaches double amidoxime ester prodrugs and provides an illustration where a simple ester prodrug did not improve oral activity of and RGD analog, whereas the corresponding amidoxime ester double prodrug resulted in a 9-fold improvement in oral absorption. (see Wang, p. 442, column 1, lines 12-20) As noted by Wang,

> *[T]his also helps to demonstrate that masking both ionizable functional groups could be a more effective way than masking only the carboxyl group in improving the oral activity of an RGD analog.*

Wang, p. 442, column 1, lines 20-24.

Wang further discloses triple prodrug strategies that have also been employed to improve the oral bioavailability of RGD analogs. Wang provides illustrations where such

triple prodrugs resulted in improved oral bioavailability relative to the parent acid, the simple ester prodrugs, or even double prodrugs. (see Wang p. 442, column 2, line 9 – p. 443, column 2, line 7.) In conclusion, Wang states

> *[A]ll of the above examples indicate that masking more than one ionizable polar functional group is indeed more effective in helping to improve the oral activity of an RGD analog than masking a single functional group.*

(see Wang p. 443, column 2, line 9 – line 13.)

It is Applicant's view that one skilled in the art, in possession of the general teachings of Wang, would be without the requisite motivation to prepare simple alkyl monoesters that mask only the carboxyl functional group in favor of the double, triple and cyclic prodrug strategies also set forth in Wang. Furthermore, even if one skilled in the art were to pursue a simple alkyl monoester approach for improving the oral bioavailability of (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1(2)*H*-tetrazole-5-yl)ethyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid, there would not be the requisite expectation of success in view of the remaining, unmasked ionizable functional groups which could negatively impact the membrane permeability of the resulting molecule, and thus its oral bioavailability.

While not raised by the Examiner during the telephonic interview held on February 1, 2007, Applicant would also like to address the remaining references that have been cited during the prosecution of the present application:

Bundgaard *et al., J. Med. Chem.,* 28(8): 979-981(1985) (Bundgaard II) is in the field of agents for ocular delivery. Further, unlike the present invention, the functional drug in this reference does not contain a free carboxylic acid group, but rather contains a cyclized lactone. The ester prodrugs that are disclosed in this reference are not merely metabolized to yield the active functional drug, but rather must first undergo cleavage of an alkyl ester moiety to an alcohol, followed by intramolecular cyclization to yield the active lactone. (See Scheme I, page 980)

Bibby *et al., Int'l J. Pharm.*, 144: 61-70, (1986) discloses butanoic, lauric, and oleic acid ester prodrugs of the anti-AIDS drug zidovudine, or AZT. However, AZT itself is not a carboxylic acid. In this case the alcohol or "ester" portion of the prodrug is the active agent that is generated after prodrug administration. Cleavage of the entire carboxyl residue is necessary to yield the functional drug. Furthermore, as indicated on page 68, column 2, lines 9-15 of Bibby, intraduodenal administration of the various prodrugs produced no statistically

significant differences in plasma AUC values of AZT, relative to administration of AZT itself.

Stinchcomb *et al.*, *Pharm. Res.*, 13(10): 1519-1523 (1996) (Stinchcomb I) discloses acetyl, propyl, butyl, and isobutyl esters of buprenorphine for transdermal administration, whereas Stinchcomb *et al., J. Pharm. Sci.*, 91(12): 2571-2578 (2002) (Stinchcomb II) discloses acetate, propionate, butyrate, valerate, hexanoate, and heptanoate esters of naltrexone for transdermal administration. Again, however, the active agent or "drug" in both of these references is not a carboxylic acid. Rather, the alcohol or "ester" portion of the prodrug is the active moiety and cleavage of the entire carboxyl residue is necessary to release the active agent. (See Figure 1 of each reference)

Thus, it is Applicant's view that Bundegard II, Bibby *et al.*, Stinchcomb I and Stinchcomb II are not analogous art references relevant to the obviousness analysis of the simple alkyl monoester prodrugs of the type of the present invention, which are converted *in vivo* to free carboxylic acid drugs.

Kao *et al.*, *Pharm. Res.*, 17(8):978-984 (2000) discloses alkyl ester prodrugs of L-Dopa for nasal delivery to avoid first pass metabolism to dopamine. However, as depicted in Fig. 3 (B) therein, plasma levels of L-Dopa did not appreciably improve following nasal administration of the methyl, butyl, pentyl, cyclohexyl, or benzyl ester prodrugs when compared to the levels achieved following administration of L-Dopa itself.

Doh *et al.*, *J. Pharm. Sci.*, 92(5): 1008-1017 (2003) discloses alkyl ester prodrugs of ketorolac for transdermal delivery. However, as depicted in Fig. 1 therein, the parent drug ketorolac, contains only one ionizable polar functional group at the carboxy terminus. As described above, the parent drug of the invention compounds contains three ionizable polar functional groups. Furthermore, nothing in Doh suggests that use of these ester prodrugs would improve the already high (90%) bioavailability of ketorolac following oral administration (described at page 1008, column 2, lines 1-2).

In summary, the references cited in support of the present rejection under 35 USC §103(a) disclose a wide variety of ester prodrug approaches including: aliphatic esters; aromatic esters; acyloxyalkyl double esters; alkoxycarbonyloxyalkyl double esters; double amidooxime ester prodrugs; double carbamoyl ethyl ester prodrugs; as well as triple prodrugs (acetate-carbamoyl-alkyl esters, carbamoyl-dialkyl esters, and hydroxyl-dialkyl esters) and coumarin based cyclic prodrugs. Regarding simple alkyl monoester prodrugs of the type of the present invention, however, the cited primary references (Bundgaard I and Wang), when taken as a whole, actually teach away from such compounds in favor of highly functionalized

esters, or double or triple prodrugs. Furthermore, to the extent that any of the cited references in fact disclose simple alkyl monoesters, these disclosures nonetheless fail to provide the requisite expectation of success in obtaining a simple alkyl monoester that improves the bioavailability of (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1(2)*H*-tetrazole-5-yl)ethyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.

In view of the discussion herein, Applicant respectfully submits that the requisite *prima facie* case of obviousness to sustain a rejection under 35 U.S.C. §103(a) does not exist in the present case. Applicant courteously requests withdrawal of the pending rejection under 35 U.S.C. §103(a) and passage of the case to allowance. In the event the Examiner intends to once again reject the present invention under 35 U.S.C. §103(a), Applicant kindly requests of the Examiner to consider each claim of the invention separately. If verbal discussion would be of any assistance in advancing prosecution of the present application, Applicant's undersigned attorney invites the Examiner to telephone him at the number provided.

Respectfully submitted,

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